

Recent Research Findings for Slowly-Progressive Insulin-Dependent Diabetes Mellitus (SPIDDM)

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Diabetes has been one of the important medical problems in the world. Diabetic patients have been increasing in developed and developing countries, and the management of diabetes has been crucial to be resolved from social and economic points of view [1]. Furthermore, diabetes has microvascular and macrovascular complications, which influence Quality of Life (QOL) and Activities Daily Living (ADL) of the patients [2]. Diabetes includes several types including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) and others. Recently, one of the medical topics would be the overlapped subtype of T1DM and T2DM, in which careful following up will be necessary for adequate diabetic treatment and management.

According to the guideline of the American Diabetes Association (ADA) and the World Health Organization (WHO), T1DM has been divided into 2 types. They are i) autoimmune diabetes (type 1A) and ii) idiopathic diabetes (type 1B) [3]. The former is characterized for its presence of autoantibodies at the onset of hyperglycemia, including anti-glutamic acid decarboxylase (GAD), anti-insulinoma-associated antigen 2 (IA2) and other antibodies [4]. In contrast, the latter is characterized by insulin dependence without evidence of autoimmunity [3].

On the other hand, there has been more detail classification of T1DM in Japan Diabetes Association (JDA). They include i) autoimmune and ii) idiopathic in the light of etiology, and iii) acute, iv) slowly-progressive insulin dependent diabetes mellitus (SPIDDM), v) fulminant in the light of onset style [5]. Patients with SPIDDM tend not to develop ketosis or ketoacidosis, and not require insulin treatment in early stages [6]. As to SPIDDM, the diagnosis is made due to a positive results for anti-glutamic acid decarboxylase antibody (GADA) or islet cell antibodies (ICA) [7].

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There were alternative medical terms concerning this disease, which are SPIDDM and latent autoimmune diabetes in adults (LADA) [8]. SPIDDM was proposed to indicate the characteristic aspect for the subjects, which had positive results for GADA and/or ICA. Clinically, they showed initially insulin independent at the onset in early stages. After that in several years, however, their insulin secretion will be impaired, leading to insulin-dependent status [9]. Thus, clinical characteristic process and status are observed in SPIDDM and LADA.

From immunological point of view, there are several diabetes-associated autoantibody (DAA) detectable in classical T1DM and SPIDDM. GADA has been the most sensitive marker in T1DM and also SPIDDM [10,11]. In contrast, insulin autoantibodies (IAA), protein tyrosine phosphatase IA-2 (IA-2A), and islet-specific zinc transporter isoform 8 (ZnT8) autoantibodies have been rather frequent in younger subjects with recent diagnosis of T1DM. However, these antibodies have been less in LADA patients [11].

According to the previous reports, GADA prevalence in normal healthy people was 0.5%-0.8% [12]. In comparison, it was 2-6% in T2DM without insulin therapy, and 11%-15% in T2DM with insulin dependent status later. From these investigation, it is suggested that GADA would be responsible for the onset of diabetes and aggravation of insulin secretion ability [13,14].

Among several types of diabetes, there has been various discussion of SPIDDM [15]. It was believed to be due to the destruction of β -cell by islet-cell autoimmunity, and be gradually progressed to an insulin-dependent status for long period. The presence of GADA has been required for the making the diagnosis of SPIDDM. However, some controversy was found concerning the GADA assay kit with radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA) [15].

There have been some reports concerning GADA measurement system. Formerly, the GADA-RIA method was actually applied for clinical medical practice. When the results were divided into high and low titers, blood C-peptide concentration was 0.73 ng/mL vs 0.68 ng/mL, respectively, which was no significance [16]. On the other hand, when comparing the antibody titers measured by GADA-ELISA between positive and negative, the blood C-peptide concentration was 0.85 ng/mL vs 2.60 ng/mL, respectively, with significant difference. From these data, the results of GADA-ELISA seem to indicate a decrease in insulin secretion ability [16].

It has been said that the endogenous insulin secretion is preserved in T2DM, while it is almost disappeared in T1DM. In fact, however, secreting small amounts of insulin has been found in T1DM by measuring ultrasensitive C-peptide assays [17]. According to the precise study for T1DM patients with long history more than 28 years, endogenous insulin secretion was detected in 80% of them [18]. Despite of these clinical data, the genesis of persistent insulin secretion in T1DM has remained unclarified in detail [19]. The progress of this research will contribute to clarify the pathophysiological mechanism of SPIDDM.

For the study of SPIDDM, there was a nationwide survey in Japan. This multi-center study was for investigating clinical and genetic characteristics of SPIDDM, under the auspices of the Japan Diabetes Society (JDS) [9]. Among the patients with SPIDDM, there is a group of the patients with non-insulin-requiring SPIDDM (NIR-SPIDDM), which was reported by Japan Diabetes Society Committee on Type 1 Diabetes Mellitus Research [9]. They compared two groups, which were 82 patients

with NIR-SPIDDM for >5 years, and 63 patients with insulin-requiring SPIDDM (IR-SPIDDM).

As a result, NIR-SPIDDM showed i) later diabetes onset, ii) higher body mass index, iii) longer duration before diagnosis, iv) less frequent hyperglycemic symptoms at onset, v) higher C-peptide, LDL-cholesterol and Triglyceride (TG) values compared to those of IR-SPIDDM. Further, NIR-SPIDDM showed vi) lower frequency of susceptible HLA-DRB1*04:05-DQB1*04:01 and vii) higher frequency of resistant HLA-DRB1*15:01-DQB1*06:02 haplotype [9].

To summarize the mentioned above, research on SPIDDM has been advanced to date. The pathophysiological characteristic changes from NIR-SPIDDM status to IR-SPIDDM several years later. From the international point of view, it is expected that the basic clinical and research results of SPIDDM will contribute to the development of medicine, society and economy of diabetes in the future.

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